Albumin-binding Auristatin prodrugs for long-term tumor regressions

Tubulin-binding drugs, such as vinca alkaloids and taxanes, have had a significant impact on clinical oncology and have generated an intense interest in the considerably more potent tubulin-disrupting agents auristatins and maytansinoids. Early clinical trials with representatives of these two drug classes, the dolastatins and maytansine, however, failed due to a lack of efficacy and/or unacceptable toxicity. They gained a revival in 2011 and 2013 with the approval of two antibody drugs conjugates, Adcetris® and Kadcyla® [1]. An intriguing question that came up was whether such highly potent drugs could be used without antibody conjugation.

Dr. Felix Kratz and his team have investigated the use of albumin, the most abundant plasma protein, as a macromolecular drug carrier with a spectrum of conventional chemotherapeutic agents for over 25 years focusing on acid-sensitive, as well as enzymatically cleavable linkers [2]. Tumor uptake of albumin is known to be mediated by the presence of albumin-binding proteins in the tumor vasculature and interstitium. The hallmark of the Kratz team’s drug delivery approach is the selective in situ binding of low molecular weight albumin-binding prodrugs to the cysteine-34 residue of circulating albumin with subsequent formation of a circulating albumin-drug conjugate. The most advanced albumin-binding prodrug is Aldoxorubicin, an acid-sensitive prodrug of doxorubicin, which has shown favorable results in phase 2 and phase 3 clinical trials against metastatic first- and second-line soft tissue sarcoma and a good safety profile with minimal cardiotoxicity in over 500 treated patients [3].

The Kratz team designed and developed albumin-binding prodrugs of auristatin E characterized by a carbonyl group introduced into the auristatin E peptide backbone, the maleimide group as the albumin-binding moiety, and a water-solubilizing aromatic linker forming a robust acid-sensitive hydrazone bond with the active drug [4]. The first decisive proof-of-concept of any drug delivery system is demonstration of in vivo efficacy. Subsequent to the detailed in vitro characterization of the two lead candidates, abbreviated AE-Keto-Sulf07 and AE-Ester-Sulf07, their antitumor efficacy was evaluated in a panel of patient- and cell-derived human tumor xenograft models (melanoma A375, ovarian carcinoma A2780, non-small-cell lung cancer LXFA737 and LXFE937, and head and neck squamous cell carcinomas) in comparison with the parent compound auristatin E. While auristatin E was essentially devoid of any antitumor efficacy except in one model, both albumin-binding prodrugs showed an anticancer efficacy inducing statistically significant partial and/or complete tumor regressions in both small tumors (130–150 mm³) and large tumors (270–380 mm³). Of note is that long-term regressions were achieved in all tested xenograft models up to 14-week post-injection.

This convincing preclinical proof-of-concept demonstrates for the first time that the body’s own albumin can be used as an effective drug carrier for the highly potent class of auristatins with reduced side effects. Translating albumin-binding drugs into the clinical setting has several potential advantages over ex vivo synthesized drug protein conjugates or other delivery systems: albumin-binding drugs are based on straightforward organic chemistry, they are chemically well-defined, and the analytical requirements for defining the pharmaceutical products are comparable to any other low-molecular weight clinical drug candidate. The beauty of the Kratz team’s work is that there was no preconceived expectation of the efficacy, as often wrongly assumed by most nanomedicine delivery systems, and his prodrug approach can be used for many different applications. The Kratz team’s approach can also be used for poorly soluble anticancer drugs which are often formulated into Cremophor EL, liposomes, or polymer micelles. The prodrug approach has been widely used mostly in oral drug delivery systems to enhance the water-solubility of poorly soluble drugs, and now it can be also useful for injectable drugs for targeted delivery. This prodrug chemistry can be used for a variety of types of drugs for enhanced efficacy, reduced side effects, and increased water-solubility. It is time for Dr. Kratz to harvest the fruits of his decades-long pursuit of albumin as an effective drug carrier.

References


Kinam Park
Purdue University
Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu